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THE CHEMICAL ORIGIN AND REGULATION OF LIFE.

INTRODUCTORY.

THE last years of the nineteenth and the first of the twentieth century, which have constituted a period of tremendous progress in physical science, have unfortunately witnessed a recrudescence of that "cult of incompetence" in biology, *vitalism*. Neo-vitalism, under the leadership of Driesch[1] in Germany and of Bergson[2] in France, asserts that the phenomena of life are not determined by law-abiding forces, but by a form of activity the effects of which are unpredictable, and which, consequently, must be regarded from a formal point of view as chaotic and beyond the range of science.

It is the purpose of the present paper to combat the thesis of the new vitalism by showing how a single physico-chemical conception may be employed in the rational explanation of the very life-phenomena which the neo-vitalists regard as inexplicable on any but mystical grounds. This conception is that of the *enzyme*, or *organic catalyst*, and it is the belief of the writer that the conception in question, with its physical and chemical corollaries, will ultimately prove adequate to the resolution of at least five fundamental mysteries of vital behavior: (1) the origin of living matter, (2) the origin of organic variations, (3) the ground of heredity, (4) the mechanism of individual development, and (5) the basis of physiological regulation in the mature organism. It is perhaps needless to say, however, that only a very meager idea of the manner in which the enzyme concept can be applied in the solution of these problems can be conveyed within the limits of a single article, and, accordingly, the writer hardly expects to satisfy all of the demands and arguments of neo-vitalism in the present paper. It must suffice here to suggest lines of thought which may later be developed more extensively.

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[1] Hans Driesch, *The Science and Philosophy of the Organism*, 1908, 2 vols. Also, *Die "Seele" als elementarer Naturfaktor*, 1903.

[2] H. Bergson, (Engl. trans.) *Creative Evolution*, 1911.

A word should be said at the outset concerning the method and point of view of the discussion which is to follow. This discussion will present no new experimental facts; it will rather compare and unite a number of such facts, which are common knowledge to all biologists, in an attempt to build up a consistent and coherent theory of the experimental field in question. Our method, then, will be *synthetic,* or inductive in the true sense of the word, instead of being strictly empirical. Very few theories can be directly verified by the observation of nature; the best one can say for a scientific hypothesis is that it is in harmony with the facts, and this harmony is what constitutes explanatory power. That the theory of enzymes is in harmony both with the phenomena exhibited by living organisms and with the principles of chemistry and physics we shall attempt to demonstrate, so far as is possible within the limits of a brief discussion; but we cannot hope to show that it is an accurate representation of reality, for this is too much to ask of any scientific theory. The only original merit which the writer cares to claim is that of seeing and recording the perfectly obvious relationships of things, when his colleagues have failed to see or else to record them.

THE ENZYME AS A CHEMICAL REGULATOR.

Modern vitalism, like its progenitors, is dualistic. It asserts that living matter is the product and expression of two fundamentally independent forms of existence, the physical and the vital. And the first difficulty which vitalism raises in the path of scientific progress in the study of life is that of the process by which protoplasm was first generated from inorganic substances. Under present conditions living matter is formed from the non-living only under the influence of other living matter; but if the mechanistic theory of life is to hold we must suppose that this has not always been the case and that far back in the past there was a time when organic bodies were formed spontaneously from dead and unorganized matter. The vitalist maintains that such a spontaneous change is inconceivable and that in order to account for the origin of living organisms one must invoke the activity of a special *regulative principle,* which even in the first instance limits and directs the mutations of physical substance so that vital phenomena at last appear. But the objections which can be made to the physico-chemical interpretation of life do not end at the beginning; simple protoplasm must be developed into complex and varied organisms, each capable not only of propagating its kind but also of giving rise to new species which shall constitute improvements upon the old.

Neo-vitalism tends for at least two reasons to reject the Darwinian doctrine of evolution by natural selection, which was formerly considered adequate to the explanation of tribal development. The first is the admitted failure of the mechanistic school of biologists to account for the *origin of variations.* Darwin referred to variations—which form the *sine qua non* of natural selection—as accidental, but qualified this reference by stating that he did not actually regard them as accidental but as due to unknown causes.[8] The modern vitalist emphasizes the unfortunate fact that these causes are still unknown. The second reason which neo-vitalism advances for its rejection of the Darwinian theory lies in the alleged fact of the *purposeful character of variations*: it is asserted that the changes which take place in the propagation of a species are not haphazard in distribution but manifest a definite teleological trend. This, say the vitalists, is due to the regulative influence of the vital force, which is also the cause of variation in general.

Mechanism in biology not only fails, in the mind of the vitalist, to account for organic variations, but it also fails, curiously enough, to explain the facts of heredity; it is inconceivable that the tiny germ-cell should contain a physical machine which shall be capable of constructing the living organism with the wonderful accuracy which is actually manifested in embryonic development. The organism is too intricate, and the raw material too indifferent to permit one to refer the elaborate processes of ontogeny to a mechanical contrivance contained within the germ; the relationship of heredity can only be accounted for by calling in a special vital principle which here, as in the pristine beginnings of life, serves to regulate the physical and chemical forces which impinge upon the germ-cell, and which thus engineers the changes by which the mature organism is built up. The necessity of postulating such a regulative force, outside of those of ordinary matter, is proven not only by the remarkable uniformities which are observable in the structure of individuals of the same species, but also by the ease—one might almost say the dexterity—with which the constructive process overcomes obstacles which are placed in its way. Cut a partly developed embryo in two and it will still produce a perfect organism. Purposeful adaptability of this sort can hardly be consistent with the mechanical regulation of development, but it is quite conceivable in connection with the operation of a semiconscious vital energy which possesses properties resembling foresight and calculation.

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[8] C. R. Darwin, *The Origin of Species*, 1859, Chap. 5, pp. 131-171.

Difficulties of a similar nature are raised by vitalism against the physico-chemical theory on the basis of normal physiology, in which there exist many cases of special organic regulation which are asserted to be inexplicable as the effects of mechanical forces acting under purely mechanical conditions. Such functions as the "regeneration of lost parts" and the general phenomena of "animal behavior" are said to demand a non-mechanical explanation. They present a type of regulation foreign to that exhibited by any physical substance.

It would seem, then, from the above review of the objections which the neo-vitalist raises against our acceptance of the physico-chemical theory of life, that these objections may be reduced to the problem of discovering a physical or chemical conception capable of accounting for the observed facts of organic regulation. Regulation seems to be the most striking active characteristic of living beings. The word "regulation" is here employed to denote the power which is shown by organisms to reach their apparent ends more or less independently of the environment in which they are placed, in fine, their capacity to neglect or leap over the difficulties which may be thrust in their way.

The necessity for such regulation first appears in connection with the problem of the origin of life. In order that the multitudinous and chaotic chemical changes taking place in the primeval oceans should have resulted in the production of definitely localizable and individual masses of even simple protoplasm, there must have appeared some regulative force which could limit or encourage these reactions in special directions, and which could maintain the individuality of the protoplasmic masses throughout long periods of continuous growth and repeated subdivision. If this regulative principle were embodied in a definite chemical substance or substances we might expect that the accidents of the process of its reproduction would lead to disturbances of its original nature, and to the consequent appearance of variations in the constitution and functions of the living bodies whose characters it served to determine.

This failure of the regulative principle to act with complete perfection would bring into the field of the struggle for existence new forms of regulation, which, if they happened to mediate valuable structures or activities, would be preserved and become the basis for further and more elaborate differentiation by the same method. The sum of all of the regulative substances thus established within the organism would constitute the physical ground of heredity and of embryological development,—a relation and process which is *par excellence* regulative in nature,—and these same physical determinants, arriving finally by their own efforts at the stage of mature or adult organization, would be capable through their regulative capacity of superintending the normal activities and special adaptations of the fully developed living being. However, in this final stage of their function, as in the first, the material regulative principles must not be expected to remain entirely uninfluenced by the disturbing physical and chemical forces which are more or less accidentally brought to bear upon them in the course of their regulative activity. Hence it may be that some features in animal, or even in plant behavior will present that same aspect of variability which appeared in the case of primitive development, and throughout the evolutionary process.

Regulation is essentially a selective activity. Out of a multitude of possible chemical and physical reactions the living organism selects only those limited few which correspond to what we call its "needs" or "purposes." Whether the meaning which we commonly attach to these words is at all significant from the point of view of science is a question, but whatever the case may be it is obvious that if we can exhibit a general and adequate chemical basis for such control we shall have smoothed out many of the difficulties which are faced by the mechanical theory of the nature and origin of living forms. This is the task which now lies before us.

The fact that all vital activity involves chemical change —and, if it is to be accounted for in naturalistic terms, must be supposed to derive all of its energy from such change—makes it necessary that we look for *a material principle of regulation having an essentially chemical nature and function.* Since it is our thesis that the enzyme constitutes such a principle, and one which if properly applied will dispell the fundamental difficulties raised by vitalism in the face of the physico-chemical theory of life, it becomes necessary that we devote a few words to the enzyme *per se.* The enzyme is an organic catalyst, and a catalyst is a substance which by its mere presence in a mixture is able to facilitate and direct the chemical changes there taking place. This directive power of a catalyst resides wholly in its singular ability to accelerate the so-called reaction velocity of specific chemical reactions.

It is a fact well known to students of chemistry that every such reaction possesses a characteristic "rate" which is constant for constant conditions of temperature, pressure, concentration, and the like. But all chemical changes appear to occur in the face of forces of resistance, which are at least comparable with friction in the case of mechanical motions, and the greater the chemical friction, the slower, of course, is the "rate" of the corresponding reaction. Now the mechanism by which catalyzers are able to accelerate or hasten reaction rates consists apparently in a reduction of the chemical friction. The catalyzer is a sort of intermolecular lubricant, which oils a specific reaction; it cannot assist the change by any energy of its own because it does no work, and remains unaltered at the end; rather, as the derivation of its name would indicate, it operates by freeing the molecules from their chemical chains and permitting the reaction to "slide." Every chemical change seeks a definite level; whether that level is found in a minute or in a century may be determined by the presence or absence of the appropriate catalyst.

Catalysis is not a mystical process. Although up to the present time no precise hypothesis has been advanced to elucidate its mechanism, this is due to lack of interest in the problem rather than to the impossibility of its solution, for the modern electrical theory of the constitution of matter suggests an explanation which is at once simple and in harmony with all existing physical and chemical principles.

The reduction of chemical friction by the presence of catalysts is so marked that reactions, such as that between cold oxygen and hydrogen, which without the catalyzer (platinum) would require thousands of years for their completion, may, with it, be finished in very short order. And to accomplish this catalytic lowering of the chemical resistance it is not necessary that very large amounts of the liberating substance be present; the effect—upon the decomposition of hydrogen peroxide — of finely divided platinum at a concentration of one part in three hundred million, is easily detectible. But small as is the quantity of catalyst which is thus effective, it could, theoretically, be entirely recovered from the solution at the end of the reaction, no matter how much peroxide had been decomposed or how long the reaction had been in process.

The relevancy of the peculiar properties of catalysts—

and in particular of enzymes—to the solution of the biological problems which we have been considering will appear more clearly as our discussion proceeds. It happens that chemical friction—which, we have said, is lowered by catalysts—is conspicuous in almost all reactions into which the compounds of carbon enter, and as everybody knows, it is carbon which constitutes the chemical basis of life. Accordingly, we should expect to find that the manifestly active nature of living beings is dependent upon catalytic processes, and this expectation is verified by empirical research. The presence of a specific catalyzer, or enzyme, in a complex solution of organic substances such as is given in protoplasm will obviously have the effect of accelerating that particular reaction with reference to which it is specific, while the other changes remain uninfluenced. When, as is the case with most organic reactions, the original changes are so slow in rate as to be practically negligible, and the specific acceleration produced by the enzyme is considerable, the effect of the latter will be to all intents and purposes the same as if it actually carried with it into the chemical arena, previously empty of change, a specific activity.

It is clear, then, how by their mere presence in complex mixtures, especially of organic compounds in solution, catalysts can exert a positive control over both the qualitative and quantitative nature of the chemical reactions which may occur in these mixtures. Since protoplasm is just such a solution as this, and since the fundamental changes taking place in living matter are chemical, the "regulative principle" which we have in our previous discussion found to be required by the most general facts of biology, may obviously be identified with the catalyst; and in this identification we shall provide a complete general basis for the explanation not only of the phenomena of regulation themselves, but of those deviations from regulation which appear in evolutionary and individual progress.

THE ENZYME AS THE CREATOR OF LIFE.

Extant theories with regard to the origin of life agree that the birthplace of living forms was the primordial ocean. In Paleozoic times the seas were universally warm, and were kept in this condition by the blanket of water-drenched air which sheathed the earth. The high concentration of carbonic acid existing in these early oceans was another factor which must have favored the original production of protoplasm, a substance fundamentally aqueous in its constitution and which even at the present time contains essentially the same variety and relative proportions of inorganic salts as are found in the sea. The idea that the primeval oceans were the cradle of life is not inconsistent with vitalism, for since life processes must have a physical substance, this substance might with all appropriateness be drawn from the warm waters of the early seas by the initial efforts of the vital force. It has been suggested, however, by Richter,[4] Arrhenius,[5] and others that the spores of life may have been transmitted to the earth within the cores of meteorites or under the pressure of starlight, an idea which enforces the conception of a permanent dualism between the living and the non-living. On the mechanistic side the theory has been advanced by Pflüger[6] that the first forms of living matter were based upon the compound cyanogen, but it is difficult to see how, upon Pflüger's hypothesis alone, this primitive protoplasm was able to reproduce and maintain itself when once formed, or how a sufficient amount of it to make up even a minute living body came to be produced at any one point.

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[4] H. E. Richter, "Zur Darwin'schen Lehre," Schmidt's *Jahrb. d. ges. Med.*, 1865, cxxvi, p. 243.—"Bericht über medicinische Meteorologie und Klimatologie," *ibid.*, 1870, cxlviii, p. 57.—"Die neueren Kenntnisse von den krankmachenden Schmarotzerpilzen," *ibid.*, 1871, cli, p. 313.

[5] S. Arrhenius, *Worlds in the Making*, 1908, Chap. viii, pp. 212-231.

[6] E. Pflüger, "Ueber die physiologische Verbrennung in den lebendigen Organismen, *Arch. f. d. ges. Physiol.*, 1875, X, p. 251.

It would be inconsistent with the general principles of evolutionary theory to suppose that protoplasm as we now know it came into being by any instantaneous process of creation; primitive living substance must have been something much more closely akin to ordinary inorganic matter than is protoplasm as we find it to-day. But primitive protoplasm must have possessed at least some of the characteristic vital properties; it must have been capable of growth and must have exhibited a certain selective activity with reference to its environment.

It is probable that the substances necessary for the original production and the nutrition of such a primordial life-form were present in the ocean-waters in rather high dilution, and there can be little doubt that the chemical changes which were requisite in order that these substances should be transformed into the native material of the organism itself were not such as could be counted upon to take place spontaneously with an appreciable rapidity. There is thus no guarantee that a rudimentary protoplasm, once formed, would exhibit the phenomenon of growth, except by virtue of some inherent properties of its own.

A little reflection will serve to show that if we are not diffident in our application of the conception of catalysis it will provide us with an explanation of life from the very start. Let us suppose that at a certain moment in earth-history, when the ocean waters are yet warm, there suddenly appears at a definite point within the oceanic body a small amount of a certain catalyzer or enzyme. Let us, moreover, imagine that the sea-water contains in solution a number of substances which react very slowly to produce an oily liquid, immiscible with water. A reaction of this character based upon probable solutes of the early seas might easily be specified. Now in the third place, we must imagine that our enzyme is related with this reaction in such a way as greatly to reduce the chemical friction which it encounters, and hence markedly to increase its rate. What will be the outcome? Why, obviously the particle of enzyme will become enveloped in the oily material resulting from the reaction, and if it happens that the original substances which enter into combination are soluble in the oil as well as in the sea-water, the little oil drop will wax greater until it is split up into smaller globules by the natural currents of the ocean. It is clear that the developing oil drop is intended to represent the origin of the first and simplest life-substance. But protoplasm, however undifferentiated, must possess the power of indefinitely continued growth, a characteristic which is apparently lacking in our oil drop, for the reason that repeated sub-division will finally exhaust the original quantity of catalytic material which is present, and which is responsible for the growth process.

We have said that enzymes, and catalysts in general have the power to assist in the production of specific chemical substances. Now there is no reason why the same enzyme should not aid in the formation of more than one substance and also why one of these substances should not be identical with the enzyme itself. A process of the last mentioned variety, in which the presence of a catalyzer in a chemical mixture favors the production of the catalyzer itself is known as *autocatalysis*. Many instances of autocatalysis have been discovered in the field of inorganic chemistry so that it cannot be regarded as in any sense a vitalistic phenomenon, although we shall find the relationships which it involves to be indispensable in the chemical explanation of vital events. This will be made evident by the manner in which the conception of autocatalysis removes the difficulties faced by our theory of the origin of protoplasm. In order that the primitive life-substance, whose original formation we have described above, should be capable of continuous growth in all of its sub-divisions it is only necessary that the enzyme about which it centers should be autocatalytic, as well as effective in the production of primitive protoplasm. In this case each new globule which is formed from the original one may carry away with it a quantity of enzyme sufficient to permit its continuous growth and reproduction.

The theory of the origin of life which we have briefly outlined above, and which is to be extended as our discussion proceeds, satisfies most of the objections which have been advanced against the ordinary chemical hypothesis. The characteristic catalytic power of the enzyme accounts for the elevation of the rate of the synthetic reaction from a practically null figure to one making possible rapid growth of the protoplasmic mass. The same catalytic property explains the localization of the reaction in a definite region, for catalysis can occur only where the catalyzer itself is present. The theory also provides a basis for the permanent growth of the primitive organism—if such we dare to call it—as well as for its reproduction, without, in general, the loss of its specific individuality.

The most fundamental objection which can be raised against the theory has reference to the source of the original enzyme. This enzyme is a very special sort of body, and consequently its fortuitous formation in the primeval oceans may be regarded as an improbable event. However, this is not equivalent to saying that it was an impossible occurrence, and since only one event of this specific kind is required by the theory during a period of time covering many millions of years, objections based upon general considerations of probability have practically no force. Chemistry must answer the question as to whether our first enzyme is possible. A very great number of different compounds must have been formed as a result of the multitudinous chemical reactions which undoubtedly took place in the primordial oceans, and there is no reason why one of these compounds should not have been just the body required to mediate the origin of living matter. The striking fact that the enzymic theory of life's origin, as we have outlined it, necessitates the spontaneous production of only *a single molecule* of the original catalyst, renders the objection of improbability almost absurd.

Now although the primitive living bodies whose hypothetical origin we have above described possessed the characteristic vital power of propagating their kind by indefinitely repeated processes of subdivision, they cannot be regarded as living in the full sense in which this term is applied to the complex substance of animal and plant cells. Primitive protoplasm was probably an almost pure chemical compound; evolved protoplasm, on the other hand, is characterized by its very lack of chemical unity. Contemporary general biology is largely a development of the conception of "simple protoplasm." But "simple protoplasm" is not simple; it is a complex, a structure, a mixture; and if we are evolutionists we cannot admit that such a substance is the ultimate ground of biological thought. "Simple protoplasm" must have a chemical history, must have been built. In the following section of this article we shall consider the process by which in accordance with the theory of enzymes, primitive protoplasm may have developed into the more advanced type now familiar to biologists. It suffices at this point if we have shown that the regulative principle of life which vitalism asserts must have existed prior to all concrete vital phenomena was not necessarily immaterial in its substance. That control of self and of environment, which the vitalist rightly regards as its defining feature, appertains to life only by virtue of the store of *enzymes* which is hidden away in protoplasm, and when one of these enzymes first appeared, bare of all body, in the aboriginal seas it followed as a consequence of its characteristic regulative nature that the phenomena of life came too.

THE ENZYME AS THE BASIS OF EVOLUTION.

In spite of the great prestige of the Darwinian theory of organic evolution, many neo-vitalists have not hesitated to assert that this theory will soon be regarded as a matter of historical interest only. The doctrine of the development of adaptive forms of life by accidental variation and natural selection—which was advocated by Darwin—seems to be the only conceivable hypothesis which is capable of explaining the origin of species in a mechanistic way, and yet it cannot be denied that this doctrine has recently met with reverses. The most important of these lies in the inability which is exhibited by its principal exponent, August Weismann,[7] to account in physical and chemical terms for the origin of variations. Darwin himself left this problem to be solved by his successors, with the single suggestion that variation might be due to an inheritance of acquired modifications. The mechanistic theory of heredity, as formulated by Weismann,[8] renders this suggestion abortive, and the alternatives of "amphimixis" and "germinal selection" which have been proposed seem upon analysis to be merely methods of begging the question. But there can be no doubt that variations do occur, and since no satisfactory physico-chemical explanation of their origin is forthcoming, the vitalist naturally propounds one which is in harmony with his own presuppositions, and then he proceeds to strengthen his vitalistic doctrine by showing that variations are in many cases distributed according to purpose rather than according to chance.

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[7] A. Weismann, (Engl. trans.) *The Evolution Theory,* 1904, 2 vols.

[8] A. Weismann, (Engl. trans.) *The Germ Plasm,* 1893.

The so-called "orthogenists"[9] find a consistent teleological directioning of variation in the evidence both of paleontology and of the modern statistical study of the grounds of evolution, a discovery which is at least formally in agreement with the Lamarckian—and anti-mechanistic—principle of development through a more or less purposeful effort on the part of the individual organism. The De Vriesian "mutation theory"[10] is also taken by some vitalists to represent an anti-Darwinistic movement, and indeed in a certain sense this is true, but—as we shall endeavor to demonstrate—the mutation theory is not inconsistent with the mechanistic view of organic nature, and may even be considered more in harmony with modern physico-chemical ideas than is the original doctrine of Darwinism.

Neo-Darwinism—which to-day opposes the vitalistic view of evolution—insists upon the primary irrelevancy of the character of variations to the demands, purposes, or needs of the varying and developing organism, and maintains that the fact of adaptation is to be explained only by reference to the "survival of the fittest." All species are subject to repeated and excessive multiplication, the individual exemplars of the species exhibiting variations from the type which are due in all significant cases to "spontaneous" alterations in the constitution of the determining germ-plasm, and which, in general, possess no predominating tendency either to assist or to injure the welfare of the organism, if anything rather the latter than the former, since there are more unfavorable possibilities than there are favorable ones. Since the original variations occurred in the constitution of the germ, and only secondarily in that of the individual organism, there is every reason why they should be reproduced in the ensuing offspring of the same germinal material. Those organisms possessing germinally determined characters which unfit them for survival will perish, and with them the malforming germ-plasm, so that at any time in the history of living species there will be a great preponderance of adaptive over non-adaptive organic forms. This is the essence of the mechanistic theory of evolution, a theory the critical weakness of which lies in its failure to account for the origin of variations.

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[9] Cf. G. H. Th. Eimer, *Organische Evolution*, 1890; and E. D. Cope, *The Primary Factors of Organic Evolution*, 1896.

[10] H. De Vries, (Engl. trans.) *Species and Varieties*, 1905.

Probably the greater number of the modern objectors to Darwinism would admit the validity of the process of development which it represents, provided only it is legitimate to adopt three fundamental hypotheses: first, that the germ-plasm actually and inevitably determines individual characters; second, that spontaneous variations in the constitution of this germ-plasm do occur and thus necessitate parallel variations in the corresponding individuals; and, third, that these variations are of such an order of magnitude as to bring about considerable differences in the adaptation of the individuals in question to the conditions of life. The dispute concerning the validity of Darwinism rests, then, upon a disagreement with reference to the ground of heredity, and more especially with regard to the possible occurrence of large and frequent spontaneous changes in the exact character of this ground —if it be material—in particular cases of descent. In a word, the solution of the vitalistic difficulties in the field of evolutionary theory will be provided in *an intelligible physico-chemical hypothesis capable of explaining both Mendelian inheritance and De Vriesian mutations.* It is our thesis that the theory of enzymes meets the requirements of this situation.

Our theory of the beginnings of life, which we have outlined in the preceding section, demands that primitive protoplasm should be composed of a single chemical substance which can be formed from the reagents present in the waters of the primeval oceans, by the intermediation of a specific *enzyme,* which latter is at the same time capable of bringing about its own reproduction by a similar, but *auto*catalytic process. The possibility and probability of the appearance in the early seas of an enzyme of this character have already been sufficiently debated. "Primitive protoplasm" was far from being what we now know as protoplasm, and which, as has been indicated, biologists often erroneously regard not only as the present but as the historical basis of life; irritability and contractility with all of their refinements and combinations are evolutionary additions to the original physiology of the vital material, due to variation and natural selection. If this is true, we may study this evolutionary process at its simplest in the development of "primitive protoplasm" into the more complex living substance which we now know. The original enzyme was the outcome of a chemical reaction, that is to say, it must have depended upon the collision and combination of separate atoms or molecules, and it is a fact well known among physicists and chemists that the occurrence and specific nature of such collisions can be predicted only by use of the so-called *laws of chance.* This does not mean that the motion of the molecules is actually at random, but only that the conditions which govern that motion are so complex and so difficult to study that we have as yet been unable to analyze them.

Now the kind of molecule—or chemical substance—which is produced by any particular molecular collision must depend upon the nature of the molecules which originally collide and upon the force and direction of the collision, and these factors, in turn, so far as we are concerned, are referable to chance. Consequently we are forced to say that the production of the original life enzyme was a chance event. But once a single molecule of this enzyme was formed its very existence *increased the probability* that further molecules of the same sort would be produced in the same locality; this is the meaning of autocatalysis. The autocatalytic process thus established does not, however, preclude the occurrence of further chance events of the same general kind as the one which produced the first enzyme; indeed, on account of the increase in chemical activity which it occasions the presence of the catalyzer decidedly favors such further events. Accordingly we have only to wait a sufficiently long time, and a second autocatalytic enzyme will appear, and this enzyme may furnish the basis of a new species of regulation in the substance which we have called primitive protoplasm, and which it was the sole duty of the original enzyme to synthetize from the oceanic solutes. The chemical reactions which are set up in the primitive living substance by the appearance of the second enzyme may be either favorable or prejudicial to its continued existence. In the former case the enzyme and the function which it subserves will be preserved by the action of natural selection; in the latter it will be destroyed together with all of those species of primitive protoplasm which contain it. In either event it constitutes a new biological variation, which, if favorable, provides the foundation of a new protoplasmic species. It would appear, then, that the *theory of enzymes provides a molecular basis for organic variation,* and as our discussion progresses it will become clear that this explanation is profoundly in harmony with the facts of biology, as well as with those of physics and chemistry.

Biometry demonstrates that the variability of organisms of a single species follows, in general, the law of error, a fact which clearly suggests, if it does not prove, that the factor controlling biological variation is that of chance, or the independent causal activity of a large number of separate material units. That variations should obey the laws of probability, and these only, is to be expected if the theory of enzymes is true, if the chances of variation are identical with those of the production, within the body of living matter, of special types of enzymic substance. Differentiation is simply the outcome of a continuation of the same process of random collision and combination which resulted in the production of the original life-forming enzyme. Since the *reproduction* of the germ-plasm is a chemical process, it can occur only by virtue of the probabilities involved in a *molecular chaos.*

The conception of the molecular chaos is one which is fundamental in modern physics and chemistry, and is based upon the idea that the heat motions of the individual particles which make up a body are relatively independent of each other both as regards direction and velocity. This implies that from the standpoint of the situation as a whole the molecules move more or less at random. Chemical reactions of any specified sort occur simply because the appropriate molecules happen to collide at the right speed, with the right side chains pointed in the right direction. If we take a large number of molecules we can be sure of a uniform result in any instance of chemical reaction. But if we consider a small number there will be certain cases in which the right molecules will not properly collide at all, other cases in which only a few appropriate collisions will occur, and still others in which all of the encounters will be favorable. Now the primitive germ-plasm—the first enzyme—and the elements of the later germ-plasms which arise under its influence, are not made up of an enormous number of molecules. The individual determining elements probably do not contain more than a few thousand molecules apiece. Hence it follows that the chances of the molecular chaos cannot be relied upon invariably to assist the controlling enzyme in its own reproduction, or autocatalysis.

Under these conditions there will of necessity creep into the germ-substance aberrant molecular formations, the presence of which will produce organic variations. Some of these new conditions will simply be negative, a failure of the original autocatalysis. Others, however, will be positive, the chance occurrence of rare orientations of colliding molecules causing the original enzyme to aid in the construction of new catalytic bodies, which may then become parts of a more complex germ-plasm; no enzyme can be regarded as absolutely specific in its catalytic relationships. Again, new enzymic substances may arise by the same process which produced the original catalyst of "primitive protoplasm," the simple uncatalyzed but fortunate collision of certain molecules contained within the living material. It should be kept constantly in mind that in the case of the production or reproduction of an autocatalytic enzyme a single molecular instance may determine a far-reaching series of chemical events; for the formation of a single molecule of such a substance by a type of collision which is perhaps very rare, will mark the only necessary beginning for a continuous catalytic reproduction of this substance, and possibly of others, throughout a period of indefinite length.

It is important to notice that the basis of evolutionary change which is provided by the theory of enzymes is one which supports an increasing complexity of germinal and organic characters. The variations which occur in the original germ-plasm do not involve the substitution of new germinal or enzymic elements in place of those already present, but consist rather in the *addition* of these new elements to the original ones. If these additions prove to possess catalytic properties which assist the organism in its struggle for existence they will be preserved; if not they will be destroyed by natural selection. But if they are preserved they will furnish the basis of an *added character* of the protoplasm and organism, for the *original* catalytic substance—being present in relatively large quantities, and so not liable to be disturbed by chance failures in the autocatalytic reaction—must also be preserved by the same selective forces; both the varied and its variation will exist alongside of each other. In this way, as time goes on, the organic forms which exist upon the earth will tend to become more and more complex.

Another consideration which is of the utmost importance, and which again reveals the powerful explanatory nature of the theory of enzymes, is that all variations of the sort which we have discussed above must be looked upon as "mutations" rather than as of the "quantitative" or "Darwinian" sort. Certain modern students of the phenomena of heredity, such as Professor Johannsen,[11] have compared organic species to chemical compounds, and in making this comparison have designated them as "bio-types." A "bio-type" seems to have the same individuality as has a specific chemical substance; different "bio-types" are separated from each other by definite qualitative intervals; in interbreeding they do not "mix" but maintain their identity, and if we are to accept the teachings of De Vries we must suppose that their origin is also characterized by discontinuous qualitative change, such as is involved in any chemical reaction. But surely this modern point of view with regard to the nature of variations—which has been made possible by the epoch-making discoveries recorded in "Mendelism"[12]—is unequivocally demanded by the theory of enzymes.

If we believe that the organs and functions of living creatures are determined in nature by the number and quality of the catalytic substances contained in the germ-cell, we must perforce hold that these organs and functions will vary in accordance with the changes which take place in this assemblage of enzymes. But since the enzymes are definite chemical compounds *all significant alterations* of this sort *must be qualitative and discontinuous.* It is not strange, then, that organic species should be readily comparable in their properties to the discrete bodies known to chemical science. The doctrine of De Vries that all effective biological variation consists in the addition or subtraction of Mendelian "unit characters" is quite unescapable in the theory of enzymes, for in that theory the "unit characters" correspond, as we shall see, to the individual enzymes of the germ-plasm. "Bio-types" are at bottom *zymo-types.*

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[11] Johannsen, *Lowell Lectures*, 1912.

[12] See, for example, R. C. Punnett, *Mendelism*, 1911.

The limits of this article are such as to render impossible a detailed description of the probable series of changes by which the mechanism of chemical variation which we have discussed above has been able, with the assistance of natural selection, to "evolve" living creatures as we now know them from the basis provided in "primitive protoplasm." The general principles which are involved are, however, clear. Each new enzyme which is generated within the life substance adds a new character. "Primitive protoplasm" possessed but one essentially vital property: the power of self-reproduction or growth. The other fundamental characteristics of developed protoplasm, irritability, contractility, and the destructive metabolism upon which they are based must be regarded as results of a long process of evolution. "Simple protoplasm," as we have insisted before, must have a complex chemical history. *There is practically no effect which is produced within living cells which cannot be referred to the presence of a suitable enzymic substance.* Divergence of characters among the many lines of descent leading from "primitive protoplasm" are, of course, to be expected, and variations in the type of metabolism which are selected in these diverging lines will lead ultimately to the foundation of two biological kingdoms: the animal and the vegetal.

In the beginning all living forms were, of course, of the single-celled or globule type. No difficulty exists in explaining the manner in which the chemical constitution of single cells could determine their cohesion into the large *cell masses* which make up the multicellular plants and animals, and the process by which the differentiated cells and cell-systems of these higher organisms are produced by the continued subdivision of an original germ-cell can also be explained in terms of enzymes. This is a subject to which we shall return in our next section.

THE ENZYME AS THE GROUND OF HEREDITY.

The difficulties which neo-vitalists urge against the mechanistic theory of heredity may perhaps be adequately summarized as follows. In the first place the germ-cell, which must be regarded as of prime importance in any mechanistic view of heredity, is said to be too small to contain a physical machine that shall be capable of determining with accuracy all of the intricacies of structure and function which are exhibited by the higher organisms; in the second place no *definite conception* has been advanced to show how such a hypothetical determining influence can exist. Weismann's theory that the manifold properties of the individual living organism are dependent upon the presence within the germ-cell from which the individual develops, of minute material units corresponding point for point with the separate characters of the organism, provides only the form and not the substance of such an explanation. It is our contention that the theory of enzymes not only removes the objection to the mechanistic account of heredity which arises from the extreme smallness of the germ-cell, but that it also provides us with an idea of *the definite chemical mechanism by which the contents of this* *cell determine the characters of the mature organism,* and by which they direct its development. The conception of autocatalysis, also, clears up the third fundamental difficulty of the physico-chemical theory: that of accounting non-vitalistically for the self-reproductive power of the germinal system. With reference to the phenomena of heredity the theory of enzymes is essentially an extension or, better, an interpretation of Weismann's hypothesis.

The theory of enzymes maintains that the causal relationship which exists between the germ-cell and the organism into which it develops, or which exists between a parent and its offspring, finds its necessary material basis in the bodily or catalytic transmission of the original enzymes of the germ to each of the ultimate cells of the mature body. Upon the assumption that the native ferments of any cell constitute its visible "nucleus," a possible description of the manner in which cell characters are thus determined by the germ-plasm is suggested by the microscopically observed facts of "karyokinesis," or the maneuvers of the nuclear substance during cell-division. This process has been incorporated by Weismann in his theory, and since it enters into the theory of enzymes in an entirely analogous manner we need not give an account of it in this article.[13] But if the cell characters are actually chemically determined by catalytic substances which are present in the nucleus, it is clear that the highly elaborate mechanism of karyokinesis, which, in each case of cell-division, divides the nucleus into two parts and bestows one moiety upon each new cell, is nicely fitted to a transmission of cell characters from ovum to body tissue.

But when with this genetic idea clearly in mind we are confronted by the enormous complexity of many multicellular organisms, we realize that if the mechanistic conception is to hold, the initial cell must be exceedingly com-

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[13] A. Weismann, *The Germ Plasm,* 1893, Chap. I, pp. 37-86.

plex; it can be no simple drop of homogeneous protoplasm, but must enfold within its tiny body a surpassingly intricate mosaic of separate characters. Moreover, throughout the successive stages of development by the segmentation of the primal ovum there must go on a sorting or sifting process in which certain characters are separated out and laid down, seeded, as it were, in definite portions of the body. We come to think of the germinal elements as submicrocosms, representing or symbolizing the organic body in detail. The ovum and the sperm must be regarded as architectural structures built up by the conjunction of a vast number of unit enzymes, which during development are taken down in successive steps and segregated in different organs and tissues where they exercise, by virtue of their catalytic power, that specific control or regulation which has so mystified modern physiologists, and has encouraged so many vitalistic diatheses of mind.

The observed facts of the relationship of heredity are such as to confirm this conception of the mosaic and zymotic nature of the reproductive elements. The phenomena first described by Mendel in 1865 present a case in point. It is noted that an organic characteristic like tallness in plant body, or the redness of blossoms, or an hereditary deformity, acts in experiments in the crossing of different varieties of a species as if it were a definite and discrete quality, which in any particular hybrid is forced either to appear or to be entirely absent, which cannot, in other words, be mixed, blended or compounded with a different character. It is this set of facts which leads to the conception of "bio-types," and which is so consonant with the demands of the De Vriesian doctrine of mutations, and also—as we have seen—with the theory of enzymes. The idea that the "unit characters" of Mendelism are, in their substantial aspect, specific enzymes embodied in the germ-cell and manifesting themselves in the developed organism, is almost inevitably suggested by the facts; many Mendelists definitely compare the "unit character" to a ferment.

The characteristic activities of any special *tissue cell* may be conceived as governed by the presence in its cytoplasm or nucleus of specific enzymes which facilitate certain types of chemical change. These are the "biophores," or life-bearers, of Weismann's theory. But it is clear that when the development of the organism is yet incomplete there will exist many more or less undifferentiated tissues, and in the cells of these we should expect to find a variegated store of biophores, presaging the further differentiation of the living stuff which is there present. Since rudimentary tissues of this sort are divisible into more or less discrete systems, as nervous, skeletal, alimentary, etc., we might expect to find a corresponding systematization among the controlling enzymes. Such groupings of biophores are called by Weismann "determinants." In a still more undeveloped state the enzymic contents of the organic cells will be even more complex, and will be divided into more comprehensive systems, which Weismann denominates "ids" and "idants." Each "id," according to the author of the theory, contains the potentialities of a complete organism; the "determinants" are units corresponding with the number of independently variable organic parts, and the "biophores," in our interpretation, are the ultimately life-regulating enzymes. It will readily be seen that the Weismannian mechanism of heredity is in perfect harmony with the elementary laws of Mendelism, and it is also consonant with the facts which have been established by the direct microscopic observation of the cell.

Upon our assumption that the "determinants," "ids," and "biophores" of Weismann, the "unit characters" of Mendelism, and the specific attributes of living matter in general are actually representations of the presence and distribution of definite enzymes or organic catalysts in the body and in the germ, what shall be the line of argument taken in an attempt to elucidate the processes through which the organic characters of living matter are developed under the influence of the original germinal ferments? Clearly the matter will not be a simple one, but nevertheless it seems advisable to mention some of the conceptions which the physiologist of development must use if he is to attempt a *zymology of heredity.* His ruling idea, of course, must be that same conception of a specialized catalyst which was outlined in the second section of this paper.

Zymology has already gone far enough for us to assert the empirically demonstrable existence of hundreds of bodies of this type. But the interrelations of enzymes with each other and with the substances whose reactions they affect are very diverse. We must recognize the possibility of—so to speak—an indefinite number of degrees of *zymicity,* from enzymes which take absolutely no part in reactions under their influence to others which are gradually or rapidly consumed by the chemical forces which they encounter. Besides ordinary catalysis we may have to deal with "negative catalysis" for certain bodies interfere with the catalytic effects of enzymes or of inorganic catalyzers. The presence of such "anti-enzymes" may be employed by the hereditary zymologist in accounting for the inactivity of enzymes which are present in tissues but which fail to produce in them their characteristic effects. The "kinases," or "co-enzymes," must also be taken into consideration. These are empirically demonstrable bodies which are capable of catalyzing catalysts, or at least of reacting with certain other bodies, "zymogens," to form enzymes. It is clear that the enzymes concerned in the development must all be capable of self-reproduction, or of autocatalysis, and in the mazes of this process may lie the explanation of many strange phenomena. The structure of any given cell—based in the last analysis upon prior enzymic activity—its component membranes and their osmotic permeabilities, must also inevitably enter into questions concerning the points of equilibrium of catalyzed reactions, etc.

Can the theory of enzymes cope with the difficulties of the problem of heredity? It is our belief that it will be able to do so. The enzyme meets perfectly the requirements which must be satisfied by any physical entity purporting to be able to form the basis of the elementary hereditary relationship. Its most characteristic effect upon chemical mixtures such as that which is presented in the almost watery constitution of the living organism is that of regulation, and it is recognized by every one that the hereditary relationship is *par excellence* one in which regulation occurs. Upon purely chemical grounds it is found legitimate to endow the enzyme with that supposedly peculiar property of life: self-reproduction or regeneration. The theory of enzymes thus satisfactorily disposes of one of the fundamental vitalistic objections to the Weismannian hypothesis as it was originally formulated, and permits us to regard one of the most characteristic functions of living matter as a purely chemical phenomenon. But the enzyme also beautifully fulfills the geometrical requirements which are made by Weismann's typical mechanistic hypothesis upon the controlling entities of the germ-plasm.

As we saw in the second section, catalytic effects are remarkable for the small quantity of catalytic substance which is required to produce them; one part of catalyst in many millions of reacting substance will often suffice to bring about a very great acceleration of the reaction velocity. It can be shown by a simple calculation that the human germ-cell is sufficiently large to contain a million molecules of specific enzymic material for each of the billion or more cells in the human organism. These million molecules of course constitute a very minute portion of matter, but since they are both catalytic and autocatalytic they may be relied upon to produce far-reaching changes in the other chemical substances which come into contact with them. The theory of enzymes complements Weismann's hypothesis in another way by showing how it is possible that the germinal determinants should actually be effective in the development of the organism. It is one thing to show that the germ-plasm may contain an element for each specific part of the body which springs from it, and quite another to explain how such a material particle can determine by purely physical laws the peculiar development of that body.

THE ENZYME AS THE BUILDER OF ORGANISMS.

The most powerful of the unfavorable criticisms which have been brought to bear upon the physical theory of life during modern times have been founded upon the results of the new science of "experimental morphogenesis," or the empirical study of individual development. In an article such as this it is impossible to present and analyze in detail the results of this new and fascinating line of investigation, but as any one knows who is acquainted with the writings of Hans Driesch,[14] the most philosophical student of the new science, the physico-chemical theory of development cannot rigidly maintain the logically simple form given to it by Weismann, if it is to harmonize with all of the facts. The manner in which the germinal determinants are distributed in the process of cell multiplication cannot be thought of as a perfectly straightforward differentiation, in which every cell-division signifies the production of a radical and permanent disparity between the enzymic constitution of the two resulting units of structure. The differentiation of cell constitution must needs be conceived as gradual, relative, and perhaps never quite complete; in many cases differentiation may be an expression of processes of chemical suppression or interference, rather than of the actual loss or exhaustion of the original determinants of the germ-cell.

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[14] H. Driesch, *The Science and Philosophy of the Organism,* 1908, Vol. I.

At first sight it may seem that a failure on the part of the mechanist to present a logically simple hypothesis of development which shall explain all of the facts places him in a rather embarrassing situation; but this is not actually the case. Indeed, quite the reverse is true. If the mechanism of development were describable in simple formulae, this fact would add cogency to the vitalistic contention that some intelligent principle had been at work in the establishment of this mechanism. The mechanist is prepared to discover in embryological processes the effects of crudely diverse means of adaptation, of both rudimentary and vestigial developmental tendencies, and of a type of correlation between internal and external forces which is—so to speak—ragged-edged and diffuse. If we adopt the point of view thus suggested we shall find that many of the objections which have been raised by vitalism against the physico-chemical theory of life, on the basis of experimental embryology, will lose much of their cogency. All of these objections are founded upon the hidden assumption that a mechanistic account of the causes of individual development must be logically simple, that if the mechanist employs catalysis in his explanations he must make no concomitant use of osmosis, that if there are material hereditary determinants in the nucleus of the cell there cannot at the same time be any such in the cytoplasm, that if these determinants have a causal efficiency in the process of differentiation and growth general physical and chemical influences are thereby ruled out.

We have offered the above generalizations in lieu of a detailed discussion of the vitalistic arguments of Driesch and other students of embryological development, not only because the limits of this article forbid such a discussion but also because the facts of "regeneration" and recovery from injury on the part of embryonic tissues have no special bearing upon the enzymic theory of heredity and development. The objections based upon these facts must be rebutted if the enzyme theory is to hold, but they are applicable to any mechanistic hypothesis whatsoever. Weismann's doctrine of germinal determinants in its simplest form assumes that there is a progressive simplification of the determining material of the body cells as individual development proceeds, and if this is what actually occurs it is of course impossible that one of these simplified cells should be able itself to generate any organic system different from or more complex than that of which it forms a homogeneous part. Thus a liver cell might be able to generate further liver cells, but it could not provide the starting point for the development of a new organism, or for the replacement of a missing limb. Certain exceptions to this apparent corollary of the Weismannian theory have been discovered in embryological research, and have been avidly appropriated by vitalism for use in its contest with the physico-chemical theory of life.

The general explanation which the mechanist will probably be forced to make of these exceptions lies in the supposition that all of the cells making up a given portion of an organism are not equally differentiated as regards their nuclear or enzymic substance, but that at every stage in the process of cell-simplification which is supposed to accompany development, certain cells are left behind and that these—since they possess an adequate complement of enzymic material—can, upon receiving the appropriate stimulus, regenerate any required "lost part." Residual or latent cells of this sort all belong to the same general type as the germ-plasm itself, which is known to coexist with the differentiated somatic cells of the organism.

It is essential that we should recognize the fact that there are a great many processes in the physiology of development, and of mature life, which are explicable upon a physical basis wholly apart from the directing and "self-determining" activities of the cell. Bionomics—the study of organic symmetry and related subjects—shows that differentiations of structure in animals and plants occur in fixed and parallel orders; the underlying facts of symmetry in the body reduce the strain upon the germ-plasm, the bilateral, radial and metameric repetitions of organic characters would not require new sets of determinants but simply reproduction of the old ones in accordance with some slightly modified symmetrical karyokinetic process. The modes of repetition, in fact, are found in many cases to depend upon purely physical and environmental conditions; the forces of growth are limited by other forces outside themselves, the laws of geometry and physics.

All of these considerations tend towards the judgment that the germ-plasm need by no means be as complex as the organism into which it develops. There are certain things which would happen to any mass of protoplasm exhibiting growth; the determinants of the cell have to react with other natural forces in the production of the organism, with its mature anatomy and physiology. But while there can be no doubt that as development goes on the events which occur in the body are determined more and more by the physical and chemical interactions of different organs and tissues, this need not be taken to mean that these events would ever have occurred if it were not for the special enzymic constitution of the germ-cell.

The differentiation of organic form in the course of individual development, and in the evolution of species, must ultimately be determined by *a control of the planes* *of cleavage* of the individual cells. This control may very well depend, in the last analysis, upon the molecular form of the germ-plasm. Identical chemical units may be combined in a great variety of ways, and the ordered decomposition of specific molecular groups may be relied upon to determine the relative directions of cleavage of the dividing cells and thus to regulate organic form even without chemical differentiation. The theory of enzymes does not place the processes of heredity and development in exclusively chemical categories; it does not dispense with the mosaic or structural factor in the germ-plasm. Indeed, when we clearly understand the meaning of chemical terms, we see that it would be impossible to eliminate this factor, even though we desired to do so. It is therefore legitimate to suppose that the determining enzymes of the germ-cell are arranged in a practically constant order, the unfolding of which regulates the form as well as the physical and chemical properties of the body.

The manner in which an enzyme may control structural changes is almost too obvious to require comment. We have noted that substances exhibiting almost any conceivable property or set of properties can be built up from the primary materials of protoplasm; the element carbon is the most versatile member of the chemical world. But the reactions which generate such specific substances from the raw material of the cell-plasm may be controlled by special enzymes, and in the event of such regulation the reactions in question will occur only in regions already containing the requisite enzymes. But the position of specified enzymes at any moment in development will be determined, among other things, by their position and chemical relationships within the original germ-cell. The most primitive and the most important case of the enzymic control of structure is found in the reproduction of the germinal mosaic itself. Since each catalytic component of the mosaic is entrusted with its own regeneration and since this regeneration can take place only in the proximity of the catalysts themselves the outcome of the autocatalytic changes must clearly be the practically perfect reduplication of the original system, both in respect to configuration and to chemical nature.

THE ENZYME AS THE GUIDE OF FUNCTION.

Modern physiology started out upon the assumption that all vital processes could be reduced to chemical and physical interactions, ultimately to a purely chemical causation, since all of the mechanical, thermal, and electrical changes which take place in the body are but the secondary expression of chemical energies, liberated in molecular reactions. The task of stating the exact chemistry of organic functions is one towards the completion of which a great deal has been accomplished; by untiring experimentation and argument we have acquired a fairly clear understanding of many of the activities of the animal and plant body. Such processes, for example, as digestion, assimilation, respiration, etc., may now be partially restated in chemical terms, and we can see how the more grossly physical changes occurring in the organism depend upon these finer molecular interactions.

But along with this scientific advance there has come ever more cogent evidence of the presence within the living body of constantly effective forces of regulation.[15] We may understand perfectly the purpose and chemical relationship of the bile—for instance—but have still to ask ourselves why it is that bile is secreted so constantly by the liver and not by the stomach, which is, and always has been, nourished by an identical chemical mixture, the blood. Moreover, how upon a purely chemical basis are we to explain the processes of growth and of repair? No doubt growth and repair involve chemical syntheses, but how are we to account for the fact that these changes are almost invariably of the right kind, and occur in the right place? It is the seemingly *teleological regulation* of chemical reactions which baffles the explanatory efforts of modern naturalistic physiology.

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[15] Cf. W. Mac Dougall, *Body and Mind*, 1912.

In many minor cases physiologists have discovered that specific bodily functions are under the control of special enzymes. This is the case with gastric and intestinal digestion, and it is seemingly true also of respiratory processes. They have even been able to go one step further and to show that the original production of the enzymes themselves is conditioned by the presence of still further enzymes of a higher order, the so-called "kinases." Here we have clearly suggested the idea that the regulation of the fundamental chemical reactions of the organism may ultimately be traced back to the original enzymic material deposited or left in the body cells during the course of embryological development, so that the control would causally revert to the constitution of the germ. If this suggestion were accepted it would not be hard to understand why this control should appear teleological, since we must perforce conclude that types of control lacking in utility would be eradicated in the struggle for existence, once they were supposed to depend upon the structure of the germ-plasm.

Is it not conceivable that most of the difficulties which are encountered by the chemical physiologist—difficulties, mainly, of accounting for certain more or less fixed types of regulation—may be cleared away by the theory of enzymes? This, indeed, is our thesis, for the enzyme is preeminently a regulator, and we have seen that in all probability it lies at the bottom of the relations of heredity and development with the processes of which the factors in mature physiology are immediately continuous.

Under appropriate circumstances enzymes may facilitate any conceivable variety of chemical change, whether it be one of synthesis or of decomposition. As we said at the outset enzymes lubricate chemical reactions so that they are able to reach their natural points of equilibrium with more than normal rapidity, and it makes no difference whether the attainment of this equilibrium point involves constructive or destructive operations. Accordingly enzymes may be the controlling factors in both phases of metabolism, the upward and the downward.

Enzymes fix the *organic position* of definite chemical changes, and in doing this determine the so-called specific energy of the organ or tissue which is concerned. The principle of specific energy is one of the broadest known to physiology, and stands for the fact that when particular masses of protoplasm are subjected to a stimulus they always respond in a characteristic and uniform way, regardless of the nature of the stimulus. If we inquire into the nature of this specific energy we find that its manifestations are most easily explicable upon the assumption that it is essentially enzymic in character, for enzymes are always specific and they are universally present in protoplasm.

There exists a good deal of physiological evidence to show that the characteristic reactions of cells depend upon the presence and nature of their *nuclei.* And, as we have already noticed, the cell-nucleus is supposed in the theory of Weismann to contain the hereditary determinants, and hence, in our hypothesis, the enzymes. Consequently we must regard the nucleus as the real connecting link between mature cell activity and the constitution of the germ, as well as between both of these and the evolutionary history of the species. But, as we have already intimated, this conception of the nucleus as the bearer of vital characters is not inconsistent with the concomitant presence of enzymic matter in the cytoplasm, or extra-nuclear portion of the cell.

But does not this physiological application of the theory of enzymes provide us with the skeleton of an explanation of that "teleological ordering" of vital phenomena which certain modern thinkers have found themselves at a loss to explain upon a physico-chemical basis? If it is true that all of the processes occurring within the living body are determined with a high degree of precision by the chemical zymotic constitution of the cell-nuclei, and if—as in our discussion of heredity and of individual development we have found reason to believe—the substance of the cell-nucleus is derived from and is chemically the same as certain portions of the original germ-plasm, how would it be possible for vital phenomena to have other than a "teleological ordering"? To speak of the geulation of organic functions as "teleological" is formally equivalent to the assertion that the processes in question are uniformly such as to conduce to the integrity and survival of the organism. But if all existing germ-plasms have been subjected, as we believe, to a rigid testing under "natural selection," the functions which they determine must perforce be of such a sort as to assist the species and the individual in their "struggle for existence."

One factor which tends to confuse the physiologist's judgment upon such matters as this is the great complexity of the bodily processes. This intricacy is especially perplexing whenever a function seems—so to speak—to possess *options,* when there are a number of ways in which a particular desirable organic change can be brought about. But this capacity which is often exhibited by organisms of "trying again" and in a different manner to consummate a certain effect cannot be brought forward as an argument against the hypothesis of chemical control which is offered in the theory of enzymes, for, suggestive as these "trial and error" methods are of conscious purpose, the number of "options" is limited, and each of these options can always be referred to components of a complex evolutionary history of the species, components of experience or selection in which the typical organism has succeeded under varying conditions of reaction, in obtaining the same result by different means. Where actions are actually random we may of course refer them to the influence of the molecular chaos which may be effective in the individual as in the species whenever, as in the process of learning, new and accidental variations in behavior prove useful.

CONCLUSION.

As we stated at the beginning, this article purports to be nothing more than a vague outline of the theory of enzymes as it is concerned with the question of the origin and regulation of organic activity. From the nature of the subject-matter which it involves such a theory must of necessity be elaborate and detailed. We have been able to indicate here merely its general principles and points of application to biological problems. It must be left to further supplementary expositions, and to controversies, to bring out the details of the theory; and this is a field of inquiry in which details are of great importance.

It has been our purpose to show that the conception of the enzyme is not only of use in the explanation of such every-day processes as digestion and fermentation but that its explanatory power reaches down into the roots of life. *Life, according to our conception, is something which has been built up about the enzyme*; it is a corollary of enzyme activity. And we have attempted to show how this might be true by exhibiting the enzyme, first, as the creator of life, second, as the basis of its development and differentiation, and, finally, as the guide of its now observable functions. We have seen that by the use of the enzyme concept we can throw light upon practically all of the fundamental problems of biology, those of the origin of living matter, of the source of variations, of the ground of heredity, and of the mechanism of vital regulation. These are the credentials of the enzyme theory of life; whether or not they will prove adequate to its acceptance the future alone can decide.

The theory of enzymes is advanced in this article in rebuttal of vitalism. Nearly all of the objections which are raised by neo-vitalists against the physico-chemical interpretation of life can be reduced to questions of the basis of vital regulation, and we have throughout striven to demonstrate that the concept of the enzyme provides us with a strictly physico-chemical mechanism of regulation, and on which is at the same time consistent with all of the fundamental peculiarities of the vital regulative principle, its self-reproductive power, its liability to variation, its physical minuteness, etc.

No doubt there are certain important points in vitalistic arguments which the enzyme theory does not directly affect. For example, we have not attempted to provide an explanation for the alleged facts of "orthogenesis," or of variation in a continuous direction. But special considerations will no doubt throw light upon questions of this sort.

Another problem which we have not touched upon is that of the origin and nature of consciousness. This is really a philosophical and not a biological issue, and its discussion involves a point of view wholly different from that of the present article. Even among vitalists the most intelligent thinkers do not confuse the problems of psychology and those of physical science.

Prof. E. B. Wilson, who is one of the foremost modern cytologists, has formulated the fundamental problems of heredity in the following four questions:[16] What is the physical basis of heredity? How is it transmitted from cell to cell? How does it transmit hereditary characters? How may it be so modified as to give rise to new heritable characters? It is our contention that in a general way the theory of enzymes satisfactorily answers all of these queries. It unmistakably provides a physico-chemical basis for fixed and definite inheritance, and for the "spontaneous" production of just those De Vriesian "mutations" which seem to be required by the modern study of the evolutionary process. The crucial problem of "Darwinism to-day" is that of the source of variations. Certainly the theory of enzymes makes obvious a solution of this problem which is not only in harmony with Weismann's hypothesis with regard to the hereditary mechanism but which, by its utilization of a well-known physical conception—that of the "molecular chaos"—decidedly strengthens the general bond between the organic and the inorganic.

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[16] E. B. Wilson, "The Problem of Development," *Science*, 1905, N. S., XXI, pp. 281-294.

In his analysis of the factors which enter into development Hans Driesch has expressed the actual fate of any specified cell of the embryo as a mathematical function of three variables: $p.v.(X) = f(s, l, E)$.[17] This means that the "prospective value," *p. v.*, of the cell X is determined by the absolute size, *s*, of the mass of which it is a part, by its position, *l*, in that mass, and by a third factor, E. In the theory of Driesch, E represents the vital principle, which he calls "entelechy," and it is his main thesis that the factor E cannot correspond with any conceivable physical or chemical entity. Driesch asserts in his "second proof of the autonomy of life"[18] that "entelechy" is "at the bottom of inheritance." The "proof" which he offers is one which is readily rebutted on the basis of the theory of enzymes, but the fact which it is important for us to notice is that Driesch's "entelechy"—which is the most clearly formulated vitalistic concept that has appeared in the history of human thought—has charge of all of the specifically regulative functions of the organism. It is the ground of every complex purposeful adaptation; in a word, it accomplishes just those tasks which we have assigned to the enzymes of the germ-plasm. And, conversely, if due allowance be made for the great structural intricacy of the reproductive mechanism as necessitated by its evolutionary history, we shall find that there is nothing which can be performed by "entelechy" which cannot equally well be mediated by the enzyme. Is it not, then, legitimate to parody the symbolism of Driesch, and to write: E = *enzyme*? That this is an equation the possibility of which the great vitalist himself will find it difficult to deny upon reasonable grounds is suggested by the results of his painstaking and altogether too exact analysis of the conditions under which "entelechy" is able to interfere with the course of physical events. In the Gifford lectures for 1908—on "The Philosophy of the Organism"—Driesch arrives at the conclusion that the point of contact between the vital principle and material changes may be found in the "activation" or release of enzymes within the protoplasm.[19] But it is a well-known fact that in many cases such an "activation" is conditioned by the presence of—so to speak—enzymes of the second order: the "kinases," which we have already mentioned as probable factors in the developmental process. It would appear, then, that the arguments of Driesch himself lead their author unconsciously to the door which, when opened, will reveal the enzyme—and not the mystical "entelechy"—as the pilot of life's journey.

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[17] H. Driesch, *The Science and Philosophy of the Organism*, Vol. I, p. 132.

[18] H. Driesch, *The Science and Philosophy of the Organism*, Vol. I, p. 224 ff.

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[19] H. Driesch, *Op. cit.*, Vol. II, p. 187.